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Review Article

Pediatric Acute Severe Hepatitis of Unknown Origin: What is New?

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Abstract

Globally, there are emerging cases of acute severe hepatitis of unknown origin in children. These cases have gathered increasing attention, owing to the development of acute liver failure in some cases that resulted in liver transplantation. This review briefly summarizes the outbreak and diagnostic criteria of the disease. We further discuss the possible causes and related mechanisms underlying its occurrence and progression, and analyze the challenges in management. Finally, this review emphasizes patient management in clinical settings and a combination of efforts to unmask the disease.

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Outbreak of acute severe hepatitis of unknown origin in children

On March 31, 2022, five children (aged 3–5 years) in Scotland were the first to be diagnosed with acute severe hepatitis without an identified origin. As of April 5, more than 10 cases of acute severe hepatitis in children under 10 years of age were retrospectively reported in Scotland, with the earliest being January 1, 2022. These emerging cases raised concerns since they outnumbered the annual cases reported in this region of the UK.[1] Globally, reports of children with acute hepatitis continue to increase (Fig. 1). As per the latest reports from the World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) on May 18,[2,3] the number of cases worldwide has increased to 576 from 28 countries. Among these countries, the UK reported 176 cases and the USA reported 180 cases. In Asia, cases have been reported from Indonesia (21 cases), Israel (12 cases), and Japan (12 cases). The distribution of reported cases is shown in Figure 2.

Clinical manifestation and laboratory testing

The clinical characteristics of the reported cases mainly include (1) age at presentation (of 1 month to 16 years), with most affected children under the age of 10 years; (2) a significant elevation of serum alanine aminotransferase (ALT) or aspartate transaminase (AST) >500 U/L; and (3) symptoms including jaundice, nausea, abdominal pain, fatigue, lethargy, and gastrointestinal manifestations, such as diarrhea and vomiting. Fever was reported less frequently; in particular, it was reported in Alabama (5/9 cases) and England (24/81) but not in Scotland. The most important laboratory finding was the absence of known hepatitis viruses (hepatitis A, B, C, D, and E viruses) in any of the reported cases. Preliminary epidemiological data have shown that there is no association between the disease and the use of drugs, exposure to toxins, COVID-19 vaccination, nor environmental factors.[2]

On April 23, 2022, the WHO issued a communiqué statement that adenovirus infection was detected in at least 74 cases. Among samples from 18 cases analyzed through adenovirus genotyping, adenovirus type 41 was identified. Three separate studies have reported the rate of adenovirus infection, as follows: Alabama (100%, 9/9), England (75.5%, 40/53), and Scotland (38.5%, 5/13) (Table 1).[1,4,5] In addition to adenovirus, systemic acute respiratory syndrome (SARS)-coronavirus-2 (CoV-2) monoinfection was detected in 20 cases via real-time PCR testing. Notably, co-infection of adenovirus and SARS-CoV-2 was detected in 19 cases. Among the nine patients in the USA, two recovered after liver transplantation and seven recovered without liver transplantation; there were no reports of mortality. Among the 43 patients in England, 3 had a full recovery after liver transplantation. By May 11, 2022, at least 11 children died outside England, including five children in Indonesia, 5 in the Americas, and 1 in Palestine.[2] The latest data jointly released by the WHO and ECDC show that the proportion of diagnosed children with acute liver failure who required liver transplantation was approximately 6%.[3]

In general, epidemiological features revealed that most patients were not vaccinated against SARS-CoV-2. Except for 2 of the 13 patients in Scotland, who had close contact with the other two affected children,[1] an obvious epidemiologic association was lacking in most cases reported in the Americas and England.

Keywords: Hepatitis; Children; Diagnostic; Mechanism; Management.

Abbreviations: ECDC, European Centre for Disease Prevention and Control; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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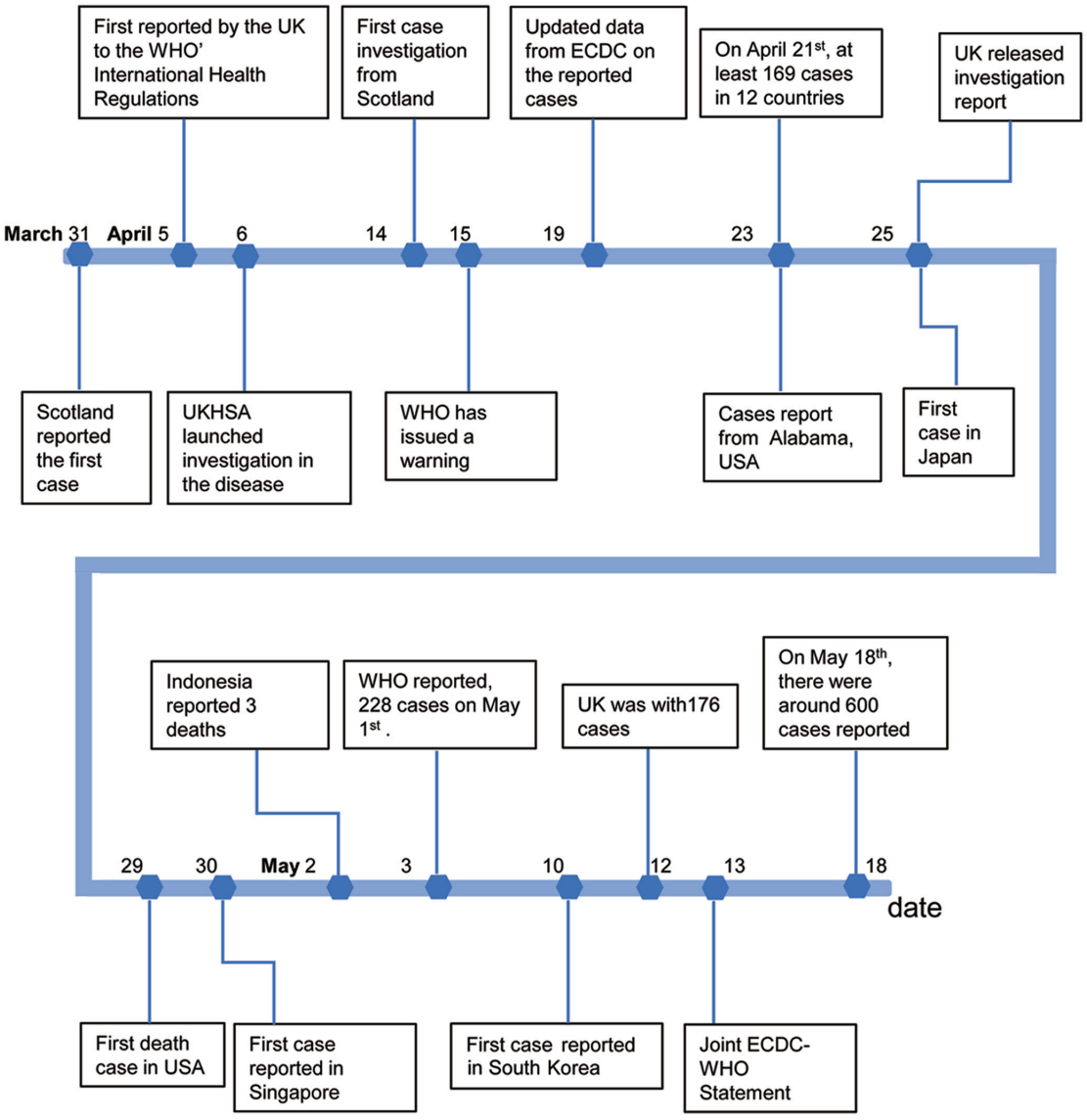

Fig. 1. Timeline of major events in acute severe hepatitis children with unknown origin from March 31 to May 18, 2022.

Differential diagnosis and treatment strategies

Differential diagnosis should be accomplished with the exclusion of other diseases, including (1) hepatophilic viral infections, such as hepatitis A, B, C, D, and E viruses; (2) non-hepatitis infections, such as those caused by rhinovirus, Epstein-Barr virus, cytomegalovirus, human herpes viruses, microvirus B19, and human immunodeficiency virus-1 (HIV-1); (3) non-viral pathogens that cause acute hepatitis, such as meningococcus and leptospira; (4) drugs or toxins, such as azithromycin and erythromycin; (5) immune-mediated liver injury, such as autoimmune liver diseases, hemophagocytic lymph histiocytosis, and gestational alloimmune liver disease; and (6) inherited metabolic liver diseases, such as hepatolenticular degeneration in children older than 5 years and in adolescents.

Children with acute severe hepatitis are at risk of disease exacerbation. Currently, there is a lack of consensus on the treatment regimen for this disease. Dynamically monitoring the biochemical parameters in the blood and clinically assessing the condition of affected children can help physicians assess disease progression promptly to modify the therapeutic strategies as needed.

Among the current treatment strategies, symptomatic therapy, such as the use of hepatoprotective drugs, is experience-based in clinic and needs to be further studied in the acute severe hepatitis with unknown origin. With this approach, in particular, physicians should be cautious when treating severe cases at risk of severe complications, such as hepatic encephalopathy, hepatorenal syndrome, secondary infection, and sepsis. Antiviral therapy should be initiated to control viral replication if the virus is identified. Liver transplantation is recommended in severe cases of acute liver failure. Whether artificial liver supportive therapy can be administered to children requires further study. If immune hyperactivation is involved in disease progression, immunomodulatory therapy, such as glucocorticoid therapy, is worth considering and may be beneficial in reducing liver injury in children.

A

	Country	Case number	Country	Case number
EU/EEA countries	Austria	2	Argentina	8
	Belgium	3	Brazil	44
	Cyprus	2	Canada	7
	Denmark	6	Costa Rica	2
	France	2	Indonesia	21
	Ireland	6	Israel	12
	Italy	35	Japan	12
	Netherlands	6	Panama	1
	Norway	4	Palestine	1
	Poland	1	Serbia	1
	Portugal	8	Singapore	1
	Spain	22	South Korea	1
	Sweden	9	America	180
	Hellenic	3		
	United Kingdom	176		

B

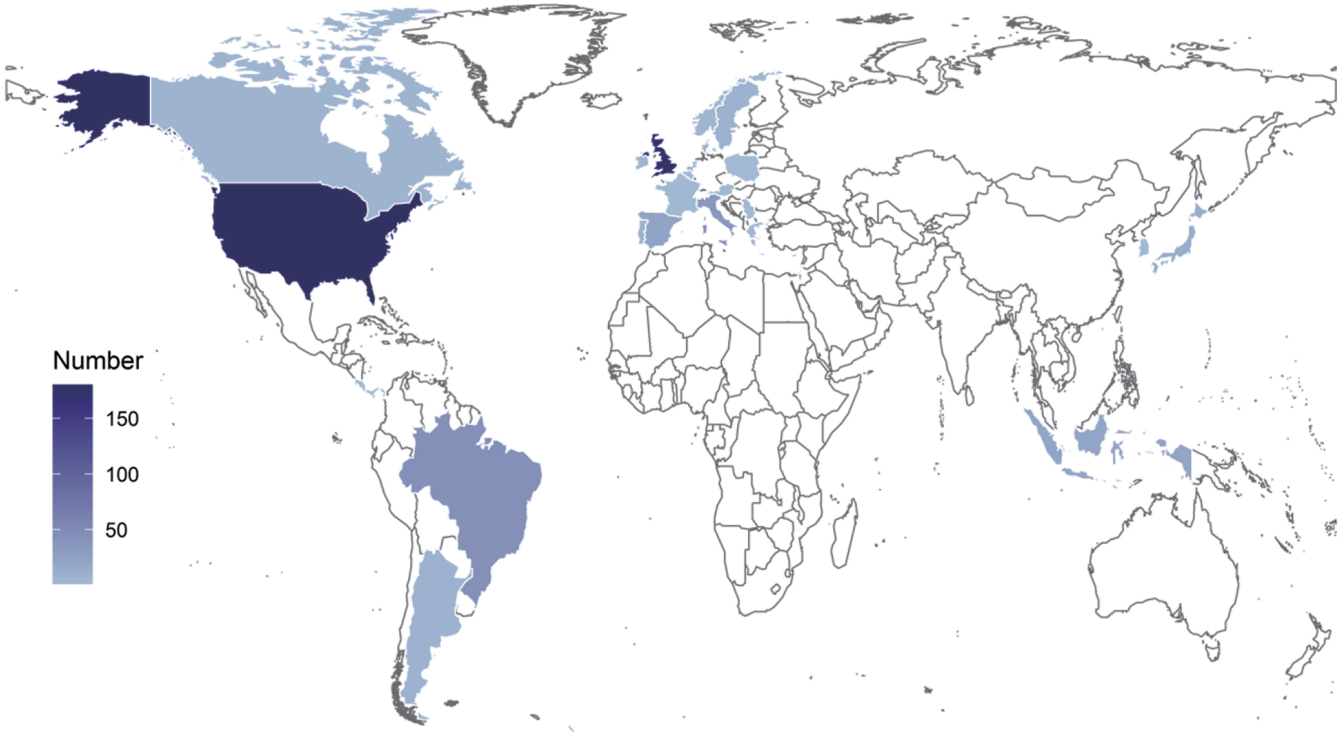

Fig. 2. Distribution of reported cases with acute severe hepatitis of unknown origin worldwide until May 18, 2022. (A) Number of reported cases up to 18th May, 2022; (B) Distribution of diagnosed cases worldwide.

Table 1. Summary of acute severe hepatitis children with unknown origin from the USA, England and Scotland respectively

	Alabama, USA	England, UK	Scotland, UK
Cases (n)	9	81	13
Median age (years)	2	3	3.9
Female/male	7/2	44/37	6/7
Liver enzymes, median (range)			
ALT (U/L)	1,724 (603–4,696)	/	/
AST (U/L)	1,963 (447–4,000)	/	/
Total bilirubin (mg/dL)	7 (0.23–13.5)	/	/
Clinical manifestations			
Jaundice	6/9 (66.7)	60/81 (74.1)	8/9 (88.9)
Abdominal pain	/	/	7/9 (77.8)
Vomiting	7/9 (77.8)	59/81 (72.8)	4/4 (100)
Pale stools	/	47/81 (58.0)	/
Lethargy	/	45/81 (55.6)	4/4 (100)
Diarrhea	6/9 (66.7)	40/81 (49.4)	4/4 (100)
Nausea	/	32/81 (39.5)	6/9 (66.7)
Fever	5/9 (55.6)	24/81 (29.6)	0/4 (0)
Upper respiratory symptoms	3/9 (33.3)	16/81 (19.8)	/
Scleral icterus	8/9 (88.9)	/	/
Hepatomegaly	7/9 (77.8)	/	/
Hepatic encephalopathy	1/9 (11.1)	/	/
Splenomegaly	1/9 (11.1)	/	/
Pathogen test (pos/total, %)			
Adenovirus	9/9 (100)	40/53 (75.5)	5/13 (38.5)
Epstein-Barr virus	6/9 (66.7)	8/45 (17.8)	/
Enterovirus/Rhinovirus	4/8 (50.0)	5/20 (25.0)	2/13 (15.4)
Norovirus	/	/	2/13 (15.4)
Cytomegalovirus	/	3/47 (6.4)	1/13 (7.7)
Metapneumovirus	1/8 (12.5)	/	/
Respiratory syncytial virus	1/8 (12.5)	2/13 (15.4)	/
Human coronavirus OC43	1/8 (12.5)	/	/
Human coronavirus NL63	/	/	1/13 (7.7)
SARS-CoV-2	0/9 (0)	10/61 (16.4)	3/13 (23.1)
Hepatitis A/B/C/E virus	0/9 (0)	/	0/13 (0)
Outcome, number (%)			
Recovered without liver transplantation	7/9 (77.8)	43/81 (53.1)	8/13 (61.5)
Recovered with liver transplantation and recovered	2/9 (22.2)	7/81 (8.6)	5/13 (38.5)*
Currently hospitalized or unknown discharge status	/	31/81 (38.3)	/
Death	0/9 (0)	0/81 (0)	0/13 (0)

For England cases: outcome at 28 days after presentation. *Including one patient who successfully underwent liver transplantation but remains in hospital.

Disease etiology: induced by pathogens or non-infectious factors?

The primary priority was to identify the cause of acute severe hepatitis in children. Although hepatitis A, B, C, D, and E viruses were excluded, other pathogens or non-infectious factors may have contributed to or resulted in the observed hepatitis cases.

Since adenovirus was most frequently detected in these

patients, it is considered a suspected pathogen. Three studies from Scotland, UK and Alabama, USA reported adenovirus positivity rates in children ranging from 39% to 100%.[1,4,5] Furthermore, the two cohorts of children (severe acute hepatitis of unknown origin or adenovirus infection) had a similar age range.[6] In addition, the England-based patients who received liver transplantation had approximately 12-fold adenovirus DNA levels than those who did not receive liver transplantation.[7] However, more robust data are still needed to support this notion. Although more than 25% of children tested positive for adenovirus infection in their respiratory, serum, or stool samples, according to a report from the ECDC,[3] there are some concerns with this hypothesis. Adenovirus positivity in throat swab samples was found in 11% of healthy children.[8–10] However, acute severe hepatitis induced by adenovirus infection is rarely observed in healthy children. The gold standard method for the diagnosis of adenoviral hepatitis is the detection of adenovirus inclusion bodies in liver biopsy samples.[11] However, adenovirus inclusion bodies were not observed in the current study. In addition, a high serum adenoviral load was absent in the reported cases. Furthermore, it is documented that ADV41 infection mainly causes gastrointestinal symptoms, such as diarrhea, and rarely causes acute hepatitis. In clinical settings, 72% of patients with adenoviral hepatitis were mainly infected with strains ADV2 and ADV5. Thus, whether adenovirus infection is the cause of the current disease needs to be further clarified.

SARS-CoV-2 is also considered a suspected (contagious pathogen) contributor. Among the 12 cases reported in Israel, 11 had a history of SARS-CoV-2 infection.[12] Studies have shown that viral RNA of SARS-CoV-2 remains in the gastrointestinal tract of affected children longer than in the respiratory tract.[13,14] Therefore, the superantigen motif in the spike protein of SARS-CoV-2, structurally similar to staphylococcal enterotoxin B, could trigger broad activation of non-specific T cells, which may lead to a multisystem inflammatory syndrome in children.[15–18] Alternatively, similar to patients with HIV-1,[19] the children previously infected by SARS-CoV-2 may have a repetitive immune activation caused by the comparatively long-term existence of SARS-CoV-2 in the gastrointestinal tract.[20] Under these conditions, children may be prone to infections by other viruses, which would contribute to the development of acute hepatitis. Previous animal studies reported that adenovirus infection significantly enhanced T cell activation mediated by superantigens. This increased the risk of toxic shock with liver damage.[21,22] Thus, continuous monitoring of SARS-CoV-2 superantigen is strongly recommended for affected children to clarify whether SARS-CoV-2 superantigen, together with infection with adenovirus or other viruses, caused the disease.

In addition to the above-mentioned viral infection, bacterial and/or fungal infection may induce hepatitis, particularly under conditions of systematic infection. However, there is no clinical evidence to date that supports this. Other non-infectious factors may be responsible for the incidence or contribute to the progression of acute severe hepatitis of unknown etiology, including genetic susceptibility, unknown toxin exposure, hepatotoxic drugs, or environmental exposure factors. Unlike highly transmissible viral infections, these factors are not contagious and cannot induce a global pandemic. Thus, there are no concerns regarding biosafety issues.

Challenges and perspectives

During the last several months, there have been increasing reports not only from the literature, WHO, and Centers for Disease Control (CDCs) of different countries worldwide but also from social/public media and many We-Media, which may overstate the risk of the disease and its potential for a global pandemic. Therefore, hepatologists should pay attention to the potential biosafety issues involved in this disease.

Some challenges must be addressed immediately. It is crucial to document unmet issues of acute severe hepatitis of unknown etiologies in children. Further epidemiological studies and whole-genome sequencing of biological samples may help identify the pathogen responsible for the disease. Close collaboration between physicians and scientists is critical to conduct basic, translational, and clinical studies to highlight epidemiology. Rapid diagnosis in potential cases is necessary for better disease management. Furthermore, it is necessary to clarify viral, immunological, and pathological mechanisms underlying acute severe hepatitis. In summary, complete control of the disease may require significant public health and medical efforts.

It may be helpful to consider the current progress in the management of adults with acute severe hepatitis when taking care of affected children. Although there are few reports, acute severe hepatitis of unknown origin was previously investigated in adult patients. Cytopenia is one of the most frequently observed clinical features. Reportedly, 49% of adult patients required liver transplantation, and 24% of them died from acute liver failure.[23] Steroid treatment may be effective for some patients. The characteristics of pediatric patients are distinct from adult patients, suggesting that clinical experience drawn from adult patients can only be used as a general reference for pediatric patients. There is an urgent need to develop effective treatment strategies for pediatric patients.

As recently recommended by the WHO, acute severe hepatitis of unknown origin in children should be actively monitored and extensively studied worldwide. Therefore, it is also necessary to investigate and assess the risk of the disease and disease progression. Moreover, routine preventive measures, such as careful hand-washing and mask-wearing, should be advocated for all children and their caregivers to avoid potential pathogenic infections. Furthermore, professional training and awareness among pediatricians and other clinicians along with development of disease management guidelines are crucial to improve the diagnosis and treatment of acute severe hepatitis of unknown origin in children.

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Conflict of interest

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Author contributions

Study concept and design (FSW, JL and JYZ), literature search and drafting of the manuscript (JL, WH and JY), critical revision of manuscript for important intellectual content, senior authorship guidance and supervision (FSW). All authors agreed with the final version of the manuscript.

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